## REMARKS

Claims 1, 4, 6, 8-10, 14, 16, 25-28, 31, 33, 37 and 39-50 are pending and under examination in the above-identified application. Without addressing the merits of the rejections set forth in the Office Action mailed October 26, 2009, Applicants have canceled claims 28, 31, 33, 39-41, and 45-50 without prejudice to Applicants' right to pursuing these claims in a related application. Claims 1, 14, 25-27 and 37 have been amended. Support for the amendments can be found throughout the specification and the originally filed claims. For example, support for the amendments to claim 1 can be found in paragraphs [032], [035], [055] and originally filed claims 25-27; support for the amendments to claim 14 can be found in paragraph [035] and originally filed claim 26; support for the amendments to claim 25 can be found in paragraph [035] and originally filed claim 25; support for the amendments to claim 26 can be found in paragraph [035]; support for the amendments to claim 27 can be found in paragraph [035] and the originally filed claim 27; and support for the amendments to claim 37 can be found in paragraph [055]. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

### Rejection Under 35 U.S.C. §112 – Written Description

Claims 1, 4, 6, 8-10, 14, 16, 25-28, 31, 33, 37 and 39-50 stand rejected under 35 U.S.C. §112 for allegedly lacking written support for the claimed compositions. The Office asserts that the specification does not provide written support for microspheres comprising at least 100, 1,000 or 10,000 different target analytes to an unlimited number. Applicants have canceled claims 28, 31, 33, 39-41, and 45-50, thereby rendering moot the rejection to these claims. Applicants respectfully disagree with the above rejection. However, in an effort to further prosecution, Applicants have amended claims 1 and 37 to recite that the first and second microspheres each comprise a plurality of 10 to 10,000 different target analytes or 100 to 1,000 different target analytes, respectively. Support for these amendments can be found in paragraph [055]. Applicants submit that the specification provides sufficient written description of the array composition of base claim 1, and all dependent claims. Reconsideration and withdrawal of the above rejection is respectfully requested.

**Rejection Under 35 U.S.C. §103**

The rejection of claims 1, 4, 6, 8-10, 14, 16, 25-28, 31, 33, 37 and 39-50 under 35 U.S.C. 103(a) for allegedly being obvious over Shuber (U.S. Patent 5,571,676) and Walt et al. (U.S. Patent 6,327,410) in view of Drmanac et al. (EP 0392546) and Hornes et al. (U.S. 5,512,439), is respectfully traversed. Applicants respectfully submit that the claimed array compositions are nonobvious over Shuber and/or Walt et al. in combination with Drmanac et al. and/or Hornes et al..

Claim 1, and thus all dependent claims thereof, is directed towards an array composition having a substrate with a surface and a population of microspheres having at least a first and second microsphere, wherein the first and second microspheres have a plurality of 10 to 10,000 different target analytes from a first and second individual, respectively, wherein the first and second microspheres have a first or second identifier binding ligand that identifies the plurality of different target analytes from the first and second individual, respectively, and wherein the population of microspheres are attached to about 1,000 to 1,000,000,000 discrete sites per $cm^2$ on the surface. Dependent claims 4 and 42 recite that the identifier binding ligands or the target analyses are nucleic acid molecules, respectively. Claims 6 and 43 further recite that the target nucleic acid molecules include genomic DNA or are single-stranded, respectively. Dependent claim 37 recites that the plurality of the first and second microspheres include 100 to 1,000 different target analytes. Dependent claims 8 and 9 recite that the substrate is a fiber optic substrate or is plastic, respectively. Dependent claims 14 and 25-27 recite that the population of microspheres are attached to various ranges of discrete sites. Dependent claim 44 recites that the microspheres are randomly distributed on the surface. Applicants respectfully submit that 1) the Office does not adequately articulate the rationale underlying the instant rejection as required by the U.S. Supreme Court's decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398; 127 S. Ct. 1727; 167 L. Ed. 2d 705, 82 USPQ2d 1385, 1395 (2007) and the recently promulgated Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc., 72 Fed. Reg. 57,526 (2007) ("Guidelines"), thus not establishing a *prima facie* case of obviousness and 2) modifying the prior art as the Office suggests to arrive at the claimed invention would cause the art to become

inoperable for its intended purpose or destroy its intended function, thus providing no motivation to one of skill in the art to combine the cited references.

One important feature of the Guidelines is an *explicit requirement* that an Examiner provide articulated reasons for the factual determinations underlying an asserted *prima facie* case of obviousness. This focus is consistent with the rule set down in the *KSR* decision that a factfinder must provide "reasons" why an invention would have been obvious to one of ordinary skill in the art. *KSR* at 1741. In explicating this aspect of the Supreme Court's decision, the Guidelines set forth several different rationales that can be used to support an obviousness rejection. The Guidelines further set forth explicit factual findings that an Examiner must articulate to support an obviousness rejection under each rationale. In the present case the Examiner has applied the "teaching, suggestion or motivation" test, identified in the guidelines as rationale (G). For an obviousness rejection based on this rationale for combining references, the Examiner *is required to articulate* the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine reference teachings; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. While it is proper for the motivation to combine to be implicit and be found in the knowledge of one of ordinary skill in the art, or, in some cases, the nature of the problem to be solved, the Office has not adequately articulated where such motivation is found, as discussed below. *KSR International Co. v. Teleflex Inc., supra.*

The Office Action states on page 5 that one of ordinary skill would have been motivated to apply the microspheres of Shuber to the microsphere array of Walt et al. with a reasonable expectation of success and for the expected benefit of simultaneous analysis of disease-causing gene sequences (Shuber, column 9, lines 18-39). However, the disclosure of Shuber cited by the Office is simply directed toward high-throughput application of their claimed invention using multiwell microtiter dishes:

> The manipulations involved in practicing the methods of the present invention lend themselves to automation, e.g. using multiwell microtiter dishes as a solid support or as a receptacle for,

> e.g. beads; robotics to perform sequential incubations and washes; and finally, automated sequencing using commercially available automated DNA sequencers. (column 9, lines 26-36)

At best, the disclosure of Shuber is directed towards high throughput methods for identifying genetic alterations in a genomic sequence by using mismatch directed cleavage of a heteroduplex DNA sample followed by sequencing (column 2, lines 36-49 and column 4, lines 29-38). Shuber describes in Examples 1-4, a method wherein 5 biotinylated primer sets were used to simultaneously amplify 5 regions of the gene of interest. These biotinylated products were then incubated with Streptavidin coated beads, followed by mismatch recognition, cleavage and sequencing to identify genetic alterations in the gene of interest. Thus, the simultaneous analysis of genetic alterations disclosed by Shuber is at best performed on only 5 different targets using multiwell microtiter dishes. This is in contrast to the array composition claimed, wherein the first and second microspheres have a plurality of 10 to 10,000 different target analytes from a first and second individual, respectively and wherein the population of microspheres is attached to about 1,000 to 1,000,000,000 discrete sites per $cm^2$ on the surface.

Applicants respectfully submit that one of ordinary skill would not be motivated to combine the microspheres of Shuber with the microsphere array of Walt et al. The simultaneous analysis described by Shuber is not performed on an individual microsphere nor is it suggested to be performed using an array density greater than a microtiter plate. Thus, Applicants submit that the simultaneous analysis of gene sequences described by Shuber does not provide motivation to combine the microspheres of Shuber with the microsphere array of Walt et al. to arrive at the claimed invention.

Applicants respectfully submit neither Shuber not Walt et al. teach or suggest an array composition wherein first and second microspheres have a plurality of 10 to 10,000 different target analytes from a first and second individual. Although the Office concedes on page 7 of the Office action that Shuber and Walt et al. do not disclose each microsphere having 100, 1,000 or 10,000 different target analytes, the Office asserts that Hornes et al. disclose microspheres for mRNA analysis via reverse transcription having 10,000 different mRNA sequences, and were well known in the art at the time of the invention (column 5, lines 11-14 and Examples 5-6, e.g. column 17, lines 35-36). The Office Action states on pages 6-7 that one of ordinary skill would

have been motivated to apply the oligo-dT microspheres of Hornes et al. to the microarrays of Shuber and/or Walt et al. with a reasonable expectation of success based on the expressed interest in mRNA analysis of Shuber (column 10, lines 9-14) and Walt et al. (column 10, lines 38-42) and for the added benefit of efficient purification of mRNA as disclosed by Hornes et al. (column 5, lines 64-65).

Applicants respectfully submit that the reference to mRNA by Shuber and Walt et al. does not provide motivation to one of skill in the art to use the oligo-dT microspheres of Hornes et al. in an array composition as claimed. Shuber discloses the following in column 10, lines 4-14:

> In this embodiment, determination of even a short sequence in the vicinity of the mismatch facilitates definitive identification of the disease-causing gene. The short sequence that is determined in the first round of sequencing can be used to design oligonucleotide probes for use in screening genomic or cDNA libraries. Other methods in which the primary sequence information can be used, either alone or in conjunction with library screening, include identification of tissue specific expression, reverse transcription-PCR amplification of mRNA, and screening of an affected population for genotype/phenotype association.

Thus, one of skill in the art would most likely view the reference to mRNA by Shuber as being directed towards using the primary sequence information obtained using the described methods to generate appropriate primers that could be used for reverse transcription-PCR amplification of mRNA. Regarding Walt et al., at best, they disclose that the bioactive agents can be nucleic acids including DNA, both genomic and cDNA, RNA or a hybrid, where the nucleic acid contains any combination of deoxyribo- and ribo-nucleotides, and any combination of bases, including uracil, adenine, thymine, cytosine, guanine, inosine, xanthanine, hypoxanthanine, isocytosine, isoguanine, and basepair analogs such as nitropyrrole and nitroindole, etc. (see column 10, lines 30-37) and the target sequence may be a portion of a gene, a regulatory sequence, genomic DNA, cDNA, RNA including mRNA and rRNA, or others (see column 11, lines 25-27). Thus, one of ordinary skill in the art would most likely view the reference to mRNA by Walt et al. as only part of a laundry list of various known nucleic acids. Applicants submit that the reference to mRNA by Shuber and the listing of RNA as a nucleic acid by Walt

et al. does not provide motivation to one of ordinary skill to use the oligo-dT microspheres of Hornes et al. in an array composition as claimed.

Furthermore, Applicants submit that applying the oligo-dT microspheres of Hornes et al. to the microsphere array of Walt et al. for efficient purification of mRNA, as the Office suggests, to arrive at the claimed invention would cause the oligo-dT microspheres of Hornes et al. to become inoperable for its intended purpose or destroy its intended function. As described by Hornes, the oligo-dTs are attached to magnetic particles and are used to hybridize to the poly A tails universally present on native eukaryotic mRNA (column 1, lines 58-63). It is the magnetic particles that provide advantages including being able to magnetically draw particles to one side of a receptacle during washing, being able to magnetically aggregate the particles at intervals to continuously monitor the material on the particles, and using magnetic aggregation to separate the particles less vigorously than traditional separation techniques such as centrifugation (column 2, lines 15-35). Hornes et al. goes on to state in column 2, lines 36-41:

> The particles are monodisperse and superparamagnetic and both these properties greatly assist the kinetics of the reactions in which the particles are involved. It is a surprising feature of the invention that the probes carried by the particles react in the various reactions virtually as rapidly as if free in solution.

Applicants submit that one of ordinary skill would be dissuaded from immobilizing the oligo-dT microspheres of Hornes et al. in a microsphere array of Walt et al. as this would result in the microspheres becoming inoperable for their intended purpose and function. If a proposal for modifying the prior art, in an effort to attain the claimed invention, causes the art to become inoperable or destroys its intended function, then the requisite motivation to make the modification would not have existed. See *In re Fritch*, 972 F.2d at 1265 n.12, 23 U.S.P.Q.2d at 1783 n.12972 F.2d 1260, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992) ("A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose."); *In re Ratti*, 270 F.2d 810, 123 U.S.P.Q. 349 (C.C.P.A. 1959) (holding the suggested combination of references improper under ' 103 because it "would require a substantial reconstruction and redesign of the elements shown in [a prior art reference] as well as a change in the basic principles under which [that reference's] construction was designed to operate").

Regarding the disclosure of Drmanac, the Office asserts that Drmanac et al. discloses a composition having a first and second microsphere, i.e. discrete particles (DP), each DP having amplification products from fragmented genomic DNA labeled with an identifier binding ligand. The Office asserts that one of ordinary skill would be motivated to modify the microspheres of Shuber and/or Walt et al. by attaching the genomic fragments encoded by identifier oligos of Drmanac et al. for the expected benefit of low cost and high throughput sequence determination (citing Drmanac et al., abstract and column 1, lines 26-32) and fast and frugal data generation (citing Dramanac et al., column 4, lines 33-38). Applicants respectfully maintain the position of record regarding the disclosure of Drmanac et al. Applicants further submit that the untested and theoretical nature of the disclosure of Drmanac et al. would have dissuaded one of ordinary skill from applying the methods proposed by Drmanac et al. to the microspheres of Shuber and/or Walt et al. to arrive at the claimed array composition. Furthermore, the methods disclosed by Drmanac et al. are directed to methods of sequencing an individual genome, with each bead containing only a single sequence, not different target analytes from different individuals as claimed. Thus, the methods of Drmanac et al. are incapable of distinguishing two different sequences on a single microsphere. Thus, one of skill in the art would be discouraged from combining Dramanac et al. with Shuber and/or Walt et al. to arrive at an array composition of different target analytes from different individuals because the very purpose of the single genome sequencing of Drmanac et al. would be confounded by the presence of polymorphisms in a mixed population from more than one individual.

In view of the above, it is respectfully submitted that the disclosure of Shuber, alone or in combination with Walt et al. and/or Drmanac et al. and/or Hornes et al. cannot render the claimed array compositions obvious under 35 U.S.C. §103(a). Therefore, in light of the amendments and remarks herein, withdrawal of the rejection is respectfully requested.

## CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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